CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-687

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

AP 6.21.04

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-687	Submission Date(s): Sept. 24, 2003
Brand Name	Vytorin™
Generic Name	Ezetimibe/simvastatin combination tablet
Reviewer	Wei Qiu, Ph.D.
Team Leader	Hae-Young Ahn, Ph.D.
OCPB Division	DPEII
ORM division	Metabolic and Endocrine Drug Products
Sponsor	MSP Singapore Company, LLC
Relevant IND(s)	IND 52,791, IND 25,742
Submission Type	Original
Formulation; Strength(s)	Oral Tablet; ezetimibe 10 mg and simvastatin 10 mg, 20 mg, 40 mg and 80 mg
Indication	Primary hypercholesterolemia and homozygous familial hypercholesterolemia (HoFH)

Table of Contents

1 Executive Summary

MSP Singapore Company, LLC (MSP), a joint venture between Merck & Co., Inc. and Schering Corporation, submitted an NDA for VYTORIN™ (also referred to as ezetimibe/simvastatin combination tablet and MK-0653A) on September 24, 2003. The proposed indication for

VYTORIN™ is the treatment of primary hypercholesterolemia and homozygous familial hypercholesterolemia (HoFH) that has been approved for the combination therapy of ezetimibe with simvastatin.

The clinical pharmacology section contains one pivotal (P039) and three pilot (P020, P024, P028) studies. Results of study P039 showed that Vytorin™ 10/10 (ezetimibe 10 mg/simvastatin 10 mg or EZ/Simva 10 mg) was bioequivalent to the co-administration of individual ezetimibe 10 mg and simvastatin 10 mg tablets in terms of AUClast and Cmax values of ezetimibe and simvastatin acid in plasma. Similarly, Vytorin™ 10/80 (ezetimibe 10 mg/simvastatin 80 mg or EZ/Simva 80 mg) was bioequivalent to the co-administration of individual ezetimibe 10 mg and simvastatin 80 mg tablets with regard to the AUClast and Cmax values of ezetimibe and simvastatin acid in plasma.

The pilot studies conducted earlier in a preliminary exploration of the combination tablet formulation were not reviewed.

1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation 2 (OCPB/DPE-2) has reviewed NDA 21-687 submitted on Sept. 24, 2003 and finds it acceptable. Recommendation and labeling comments should be conveyed to the sponsor as appropriate.

1.2 Phase IV Commitments

None.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Relative Bioavailability of Vytorin™ Compared to Co-administration of Individual Tablets:

Relative bioavailability of Vytorin™ 10/10 was compared to co-administration of ezetimibe 10 mg and simvastatin 10 mg tablet. Ratios (Vytorin™ 10/10: ezetimibe 10 mg plus simvastatin 10 mg) of least-square means for AUClast and Cmax of ezetimibe were 94.2% and 89.4%, respectively. Ratios (Vytorin™ 10/10: ezetimibe 10 mg plus simvastatin 10 mg) of least-square means for AUClast and Cmax of simvastatin acid were 105.6% and 105.8%, respectively. Since the 90% confidence intervals of AUClast and Cmax ratios were within the 80% - 125% range, it was concluded that Vytorin™ 10/10 and co-administration of ezetimibe 10 mg and simvastatin 10 mg tablets were bioequivalent.

Relative bioavailability of Vytorin™ 10/80 was compared to co-administration of ezetimibe 10 mg and simvastatin 80 mg tablets. Ratios (Vytorin™ 10/80: ezetimibe 10 mg plus simvastatin 80 mg) of least-square means for AUClast and Cmax of ezetimibe were 101.4% and 96.9%, respectively. Ratios (Vytorin™ 10/80: ezetimibe 10 mg plus simvastatin 80 mg) of least-square means for AUClast and Cmax of simvastatin acid were 88.3% and 104.0%, respectively. Since the 90% confidence intervals of AUClast and Cmax ratios were within the 80% - 125% range, it was concluded that Vytorin™ 10/80 and coadministration of ezetimibe 10 mg and simvastatin 80 mg tablets were bioequivalent.

2 Question Based Review

2.1 General Attributes

Q. What is the formulation of the to-be-marketed drug product?

The to-be-marketed combination tablets containing ezetimibe and simvastatin are available in 4 dosage strengths consist of 10 mg ezetimibe and 10 mg, 20 mg, 40 mg, or 80 mg simvastatin (**Table 1**). The ezetimibe content (10 mg) remained constant throughout all dosage strengths. The fixed amount of ezetimibe was compensated with lactose monohydrate. Combination tablets were formulated to be exact weight multiples with respect to simvastatin (10% of total weight for all 4 dosage strengths).

Table 1

Final Market Ezetimibe/Simvastatin Combination Tablet Formulations

Composition	Unit strength (mg/tablet)			
	EZ/Simva 10 mg	EZ/Simva 20 mg	EZ/Simva 40 mg	EZ/Simva 80 mg
Ezetimibe	10.00	10.00	10.00	10.00
Simvastatin MF	10.00	20.00	40.00	80.00
Microcrystalline cellulose				
Hydroxypropyl methycellulose				
[redacted]				
Croscarmellose sodium				
Lactose monohydrate				
Citric acid monohydrate				
BHA				
Propyl gallate				
Magnesium stearate				
[redacted]				
Purified Water				
Tablet weight (mg)				
[redacted]				

Q. Was the proposed to-be-marketed formulation used in the pivotal clinical trials?

Yes. Batches 0653AOCT003B003 for EZ/Simva 10 mg and 0653AOCT003E003 for EZ/Simva 80 mg used in the pivotal pharmacokinetic study (P039) have the same formulation as the final market composition of the ezetimibe and simvastatin combination product.

2.2 General Clinical Pharmacology

Not applicable.

2.3 Intrinsic Factors

Not applicable.

2.4 Extrinsic Factors

Not applicable.

2.5 General Biopharmaceutics

Q. What is the relative bioavailability of Vytorin™ tablet compared to co-administration of individual tablets?

The Vytorin™ 10/10 is bioequivalent to the co-administration of individual tablets of ezetimibe 10 mg and simvastatin 10 mg. The Vytorin™ 10/80 is bioequivalent to the co-administration of individual tablets of ezetimibe 10 mg and simvastatin 80 mg.

The relative bioavailability of the Vytorin™ 10/10 and Vytorin™ 10/80 tablets from the [redacted] of the proposed commercial batch size) versus co-administration of individual ezetimibe and simvastatin tablets was evaluated in study 039. This was an open-label, randomized, 2-part, 2-period, crossover study. One hundred ninety-two healthy subjects were assigned to Part I or Part II. Part I included treatments A and B, and Part II included treatments C and D.

Treatment A-single doses of the ezetimibe 10 mg tablet and simvastatin 10 mg tablet given concomitantly;

Treatment B-a single dose of Vytorin™ 10/10;

Treatment C-single doses of ezetimibe 10 mg tablet and simvastatin 80 mg tablet given concomitantly;

Treatment D-a single dose of Vytorin™ 10/80.

Subjects received all treatments after an overnight fast. There was a 14-day washout interval between treatment periods within each part of the study. Blood samples for determination of plasma ezetimibe, total ezetimibe, simvastatin acid, and simvastatin concentrations were collected up to 96 hours after drug administration in each treatment period. Ninety-six subjects enrolled in each part of the study, where 94 subjects and 91 subjects completed Part I and Part II, respectively. The pharmacokinetic parameters and statistical analysis results are summarized in **Table 2**.

Table 2. Summary of Pharmacokinetic Parameters and Statistical Analysis

Analytes	Geometric Mean Combination Tablet			Geometric Mean Co-administered Tablets			Geometric Mean Ratio (90% CI) Combination/co-administration	
	AUClast (ng.hr/mL)	Cmax (ng/mL)	Tmax (hr)	AUClast (ng.hr/mL)	Cmax (ng/mL)	Tmax (hr)	AUClast	Cmax
Part I								
Ezetimibe	75.94	3.59	5.0	80.62	4.02	5.0	**0.94 (0.90, 0.99)**	**0.89 (0.83, 0.96)**
Simvastatin acid	4.30	0.55	5.0	4.08	0.52	5.0	**1.06 (0.97, 1.15)**	**1.06 (0.97, 1.15)**
Total ezetimibe	646.0	68.01	1.0	662.85	74.76	1.0	0.97 (0.93, 1.02)	0.91 (0.85, 0.98)
Simvastatin	7.49	2.70	1.0	6.12	2 13	1.3	1 22 (1.12, 1.34)	1.27 (1.16, 1.38)
Part II								
Ezetimibe	76.97	4.62	2 0	75.70	4.74	1.5	**1.01 (0.96, 1.07)**	**0.97 (0.89, 1.05)**
Simvastatin acid	40.12	4 30	5.0	45 23	4.11	5.0	**0.88 (0.81, 0.96)**	**1.04 (0.95, 1.13)**
Total ezetimibe	682.2	76.08	1.0	688.7	83.18	1.0	0.99 (0.94, 1.04)	0 91 (0.85,0.98)
Simvastatin	84 86	18.85	1.0	102.93	17.94	1.5	0.85 (0 76, 0.94)	1.08 (0.96, 1 21)

Part I: EZ/Simva 10 mg or ezetimibe 10 mg plus simvastatin 10 mg

Part II: EZ/Simva 80 mg or ezetimibe 10 mg plus simvastatin 80 mg

In Part I, since the 90% confidence intervals of Geometric Mean Ratio (GMR) for AUClast and Cmax of plasma ezetimibe and simvastatin acid concentrations fell within the bioequivalence bounds 0.80 to 1.25, Vytorin™ 10/10 is bioequivalent to the co-administration of individual tablets of ezetimibe 10 mg and simvastatin 10 mg.

Similarly, in Part II, since the 90% confidence intervals of GMR for AUClast and Cmax of ezetimibe and simvastatin acid fell within the bioequivalence bounds 0.80 to 1.25, Vytorin™ 10/80 is bioequivalent to the co-administration of individual tablets of ezetimibe 10 mg and simvastatin 80 mg.

DSI inspection (Appendix 4.4) raised an issue of unjustified re-analysis of certain blood samples for ezetimibe concentrations. The reviewer conducted a bioequivalence test using the original assay values and found little consequence to the assessment of bioequivalence.

Q. Was the dissolution method and specification adequately justified?

The proposed dissolution method using USP Apparatus II (paddles) at 50 rpm [redacted] and specification of not less than [redacted] in 20 minutes for both ezetimibe and simvastatin is acceptable.

This dissolution method is the same method used for Zocor (simvastatin) tablets. It is similar to the existing dissolution method for ezetimibe in terms of using USP Apparatus II (paddles) at 50 rpm and similar concentration of SDS. The major difference is the buffer system (**Table 3**).

Table 3. Comparison of Dissolution Methods for Ezetimibe and Simvastatin Tablets

	Ezetimibe tablet	Simvastatin tablet
Agitation Speed	USP Apparatus II (paddles) 50 RPM	USP Apparatus II (paddles) 50 RPM
Medium	[redacted]	

The dissolution data of EZ/Simva tablets using the proposed dissolution method are shown in **Figure 1** and **Table 4**.

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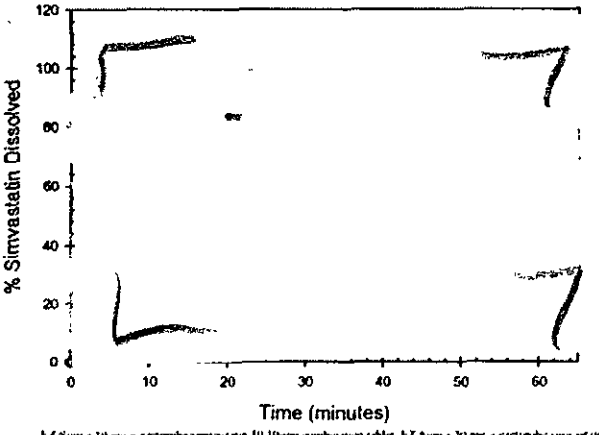
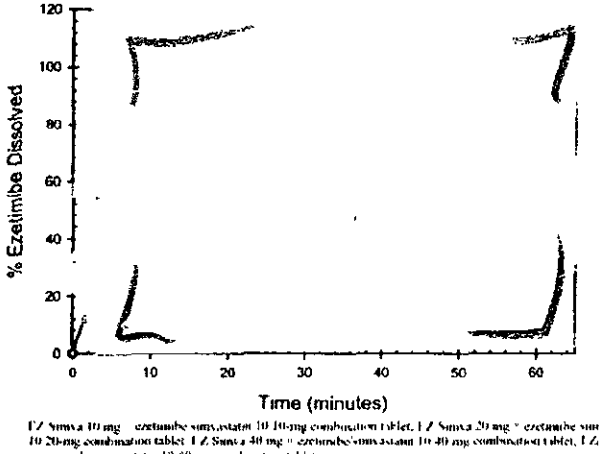


EZ/Simva 10 mg = ezetimibe simvastatin 10/10-mg combination tablet, EZ/Simva 20 mg = ezetimibe simvastatin 10/20-mg combination tablet, EZ/Simva 40 mg = ezetimibe simvastatin 10/40-mg combination tablet, EZ/Simva 80 mg = ezetimibe simvastatin 10/80-mg combination tablet



EZ/Simva 10 mg = ezetimibe simvastatin 10/10-mg combination tablet, EZ/Simva 20 mg = ezetimibe simvastatin 10/20-mg combination tablet, EZ/Simva 40 mg = ezetimibe/simvastatin 10/40 mg combination tablet, EZ/Simva 80 mg = ezetimibe simvastatin 10/80-mg combination tablet

Figure 1. Dissolution Profiles of EZ/Simva 10 mg, 20 mg, 40 mg, and 80 mg.

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Table 4. Comparison of Dissolution Profiles of EZ/Simva 10 mg, 20 mg, 40 mg, and 80 mg

Tablet Strength	Study Number	Formulation Number	N	Time, min	Ezetimibe Mean, %	Ezetimibe Range, %	Ezetimibe RSD, %	Simvastatin Mean, %	Simvastatin Range, %	Simvastatin RSD, %
EZ/Simva 10 mg	P039	[redacted]	12	10	83	[redacted]	5	85	[redacted]	5
			12	15	96		3	96		3
			12	20	100		2	100		2
			12	30	100		2	100		2
EZ/Simva 20 mg	None		12	10	72		6	74		6
			12	15	90		3	91		3
			12	20	97		1	97		1
			12	30	99		1	99		1
EZ/Simva 40 mg	None		12	10	76		7	76		7
			12	15	89		4	89		4
			12	20	95		2	94		2
			12	30	98		1	97		1
			12	45	100		1	99		1
			12	60	100		1	99		1
EZ/Simva 80 mg	P039		12	10	67		9	69		8
			12	15	84		5	85		5
			12	20	92		3	92		3
			12	30	97		2	97		1
			12	45	99		1	98		1
			12	60	99		0	98		0

EZ/Simva 10 mg = Ezetimibe/simvastatin 10/10-mg combination tablet, EZ/Simva 20 mg = Ezetimibe/simvastatin 10/20-mg combination tablet, EZ/Simva 40 mg = Ezetimibe/simvastatin 10/40-mg combination tablet, EZ/Simva 80 mg = Ezetimibe/simvastatin 10/80-mg combination tablet

Comparison of the dissolution profiles of the combination tablet reveals that the EZ/Simva 10 mg tablets (smallest) dissolves the fastest and the EZ/Simva 80 mg tablet (largest) dissolves the slowest of the combination tablets. The intermediate dosage forms (EZ/Simva 20 mg and 40 mg) dissolve slower than EZ/Simva 10 mg and faster than EZ/Simva 80 mg.

On average all strength tablets dissolved more than [redacted] in 20 minutes for both ezetimibe and simvastatin components. The dissolution specification of not less than [redacted] in 20 minutes is acceptable.

Q. Can the combination tablets EZ/Simva 20 mg and EZ/Simva 40 mg be granted biowaiver?

Yes. Biowaiver can be granted to the combination tablets EZ/Simva 20 and 40 mg based on the followings:

The formulations are essentially dose weight multiples for simvastatin and excipients with the exception that the fixed dose ezetimibe is compensated with lactose monohydrate.

Comparison of the dissolution profiles of the combination tablets showed that the EZ/Simva 20 mg and 40 mg tablets dissolved slower than EZ/Simva 10 mg and faster than EZ/Simva 80 mg.

A bioequivalence study was conducted with the lowest (EZ/Simva 10 mg) and highest (EZ/Simva 80 mg) strengths and results showed that combination product was bioequivalent to co-administration of individual tablets.

In summary, in vivo BE studies for EZ/Simva 20 and 40 mg tablets can be waived.

2.6 Analytical Section

Q. Was the analytical method adequately validated?

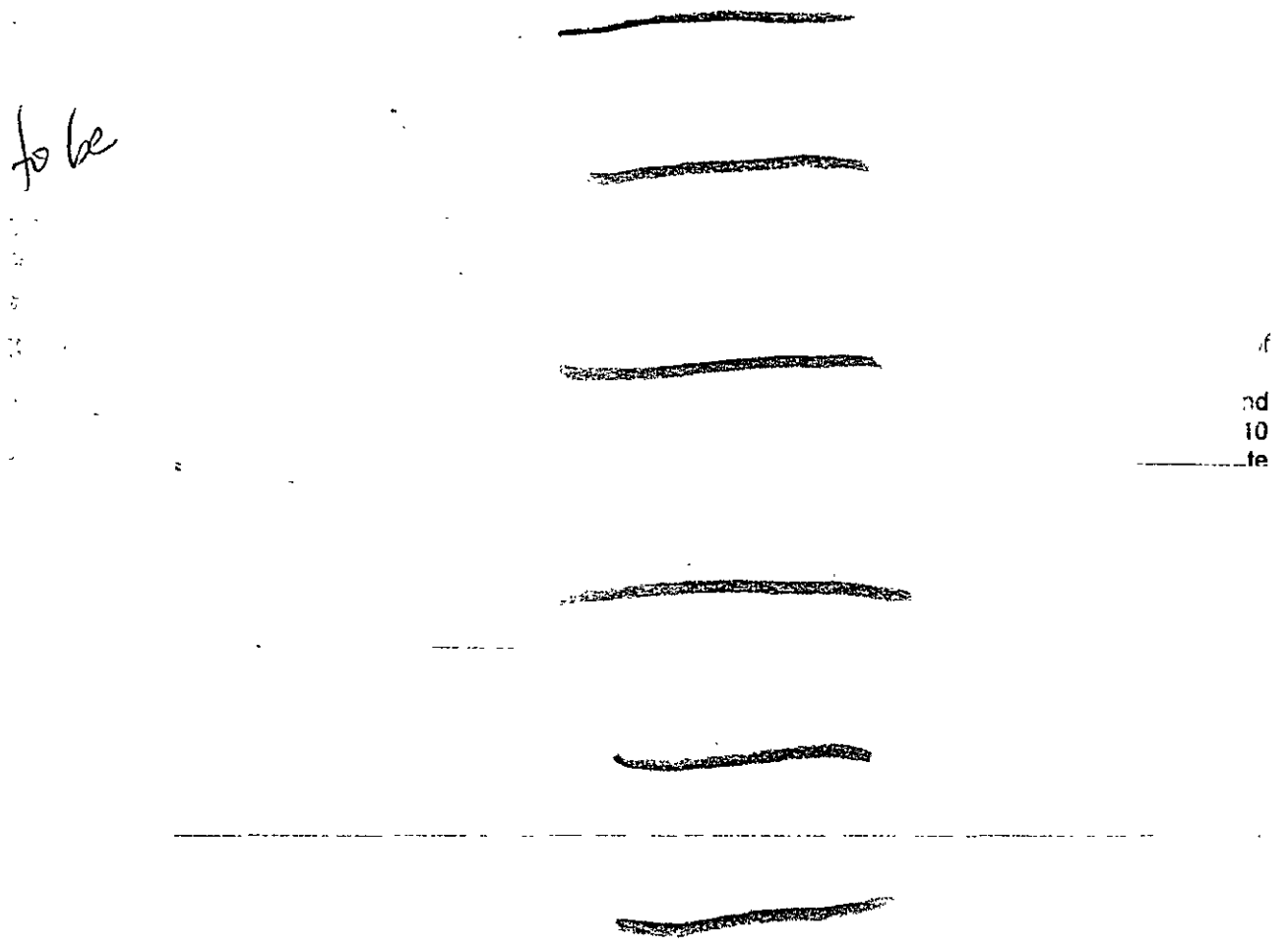
Plasma concentrations of simvastatin acid and simvastatin were determined according to a liquid chromatographic-[redacted] (LC/MS/MS) procedure. The lower limit of quantitation (LOQ) for both simvastatin and simvastatin acid was [redacted] with a calibration range of [redacted] The overall assay precision was from [redacted] CV for

simvastatin acid and from [redacted] CV for simvastatin. Accuracy ranged from [redacted] of nominal values for simvastatin acid and from [redacted] for simvastatin.

Plasma concentrations of ezetimibe and total ezetimibe were determined by [redacted] using validated high performance (LC-MS/MS) methods. The LOQ for ezetimibe and total ezetimibe were [redacted], respectively. The analytical ranges of quantitation were [redacted] for ezetimibe and total ezetimibe, respectively. The overall assay precision was from [redacted] for ezetimibe and from [redacted] for total ezetimibe. Accuracy ranged from [redacted] of nominal values for ezetimibe and from [redacted] for total ezetimibe.

3 Detailed Labeling Recommendations

[redacted]



4 Appendix

4.1 proposed labeling

(B)

Number of Pages Redacted 28

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Draft Labeling
(not releasable

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THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

20 pages

4.4 DSI Inspection Memo

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 13, 2004

TO: David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
(HFD-510)

FROM: John A. Kadavil, Ph.D.
Michael F. Skelly, Ph.D.
Nilufer M. Tampal, Ph.D.
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D.
Associate Director - Bioequivalence /S/ 5/20/04
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIRs Covering NDA 21-687,
Vytorin® (Ezetimibe/Simvastatin) Tablets,
Sponsored by MSP Singapore

At the request of HFD-510, the Division of Scientific Investigations conducted audits of the clinical and analytical portions of the following bioequivalence study:

> **Protocol # 039:** An Open-Label, Multicenter, Randomized, 2-part, 2-period, Crossover Study to Evaluate the Definitive Bioequivalence after Concomitant Administration of Single Doses of Ezetimibe (SCH 58235, 10 mg) and Simvastatin (10 mg or 80 mg) as Individual Tablets (i.e., Ezetimibe Tablets and Simvastatin) and Final Market Image (FMI) of the Ezetimibe/Simvastatin 10/10 and 10/80 Fixed Dose Combination Tablets in Healthy Adult Subjects.

The clinical portions of the study were conducted at [redacted]

The analytical portions of the study were conducted at Merck Research Laboratories, West Point, PA (simvastatin) and [redacted] (ezetimibe).

Following the inspection at [redacted] (2/24/04 - 2/26/04), no Form FDA 483 was issued. Following the inspections at [redacted]. (1/07/04 - 1/13/04), Merck Research Laboratories (12/15/04 - 12/19/04), and [redacted] (2/02/04 - 2/05/04), Forms FDA 483 were issued. The objectionable findings and our evaluations are as follows:

[redacted]

1. **Failure to maintain adequate case histories for several subjects, specifically case report forms.**

   A copy of the case report form was not maintained on site for eight study subjects. [redacted] obtained the CRFs from the sponsor for inspection. However, there were no contradictions between the sponsor's copies of the CRFs and the supporting source documents stored on site.

   [redacted] agreed to implement procedures to prevent this deficiency in the future.

Merck Research Laboratories, West Point, PA

1. **Failure to retain the original raw data for laboratory operations and observations, and correspondence for the study.**

   Study-related events were recorded as word-processing files. The files were over-written during subsequent editing, thereby obscuring the times and dates of entries, as well as the identity of individuals who made the entries. The accuracy and completeness of these records cannot be confirmed.

   Many records of internal and external correspondence regarding the study were not maintained at the facility. Thus, unknown amounts of correspondence were unavailable for inspection.

2. **Failure to consistently integrate chromatograms for calibrators, quality controls (QCs), and study samples.**

   Analysts used different integration parameters to process chromatograms in individual analytical runs, for

similar concentrations of simvastatin (SV) and simvastatin acid (SVA). This resulted in errors of 25% or less, mainly at lower concentrations. Although this practice is objectionable, there is little consequence to the assessment of bioequivalence.

3. **Failure to use concentrations of calibrators and QCs relevant to the expected concentrations of study samples.**

   The QC concentrations used in the study were 0.1, 20, and 40 ng/mL for SV and SVA. The maximum observed concentrations for Part I of the study were 15.66 ng/mL SV and 4.97 ng/mL SVA. Therefore, accuracy was only demonstrated at two concentrations, rather than the three concentrations recommended in FDA guidance.

4. **Failure to validate the procedure of diluting samples with SV concentrations greater than 50 ng/mL, up to 290 ng/mL SV.**

   Analysts did not include dilution QCs in runs with diluted study samples to validate runs with diluted samples. Because the lactone-lactol equilibrium is influenced by protein-binding, the validity of dilution should have been demonstrated.

5. **Failure to follow procedure DM-402J, in that some analytical runs used different amounts of SV internal standard.**

   The inspection revealed some runs with calibration slopes different from the theoretical 0.1 mL/ng. Examples include the analytical runs by analysts [redacted] between [redacted] Documentation for preparing the internal standard working solutions was incomplete, but [redacted] recalled using a partially thawed and thus unmixed SV stock solution to prepare the internal standard working solutions on at least one occasion.

   Because the QCs were accurately measured in these runs, the error in preparing the internal standard working solutions has no consequence. However, the firm needs to correct deficiencies in documentation.

1. **Failure to justify the re-analysis of subject samples with original results that were acceptable.**

   Schering-Plough (which managed the [redacted] contract) requested reassay of about 55 subject samples for ezetimibe concentrations. Schering-Plough provided no justification for the requested reassays, and [redacted] did not attempt to obtain it (Form 483, item 4). Data from acceptable runs were rejected and replaced with data from the repeat runs. Approximately 36% of the reassayed samples had concentration values that differed from the initial values by more than 15%. [redacted] did not investigate the source of the unreliable data.

2. **All study related correspondence is not maintained with study records.**

   For [redacted] Project AA01708-SDB the correspondence between the sponsor and [redacted] for the requested repeats was not filed with the study records. The firm needs to correct deficiencies in documentation.

Conclusion:

Following our evaluation of the inspectional findings, DSI recommends that:

1. The analytical data from Merck Research Laboratories can be accepted. However, the record keeping practices were inadequate in that raw data, such as records for preparation of solutions and reagents, extractions of calibrators, QCs, and study samples, and correspondence were not maintained. If the firm does not rectify their record keeping practices, future data could be recommended for rejection. DSI recommends that the review division mention the incomplete data and correspondence, and communicate expectations for proper record keeping in future studies in a letter to the firm.

2. Because the reason for reassaying samples for ezetimibe was not documented, the original assay values and not the reassay values at [redacted] should be used for bioequivalence determination.

After you have reviewed this transmittal memo, please append it to the original NDA submissions.

/S/

John A. Kadavil, Ph.D.

/S/

Michael F. Skelly, Ph.D.

/S/

Nilufer M. Tampal, Ph.D.

Final Classifications:
NAI - [redacted]
VAI - [redacted]
VAI - Merck Research Laboratories, West Point, PA
VAI - [redacted]

cc:
HFD-45/RF /S/
HFD-48/Skelly(2)/Tampal(2)/Kadavil(2)/Himaya/CF
HFD-510/Orloff/NDA 21-687/IND 65-066 /faxed to V. Jimenez 5/20/04
HFD-870/Qiu
HFR-SW1540/Martinez
HFR-SE2560/Collado
HFR-CE1515/Matusovsky
HFR-SW1575/MacInnes
Draft: NMT 3/15/04, JAK/MFS 5/13/04
Edit:
DSI: 5496; O:\BE\EIRCOVER\21687mps.vyt.doc
FACTS: 481316, 476024

Atts:
FDA-483, [redacted]
FDA-483, Merck Research Laboratories
FDA-483, [redacted]

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Wei Qiu
6/18/04 02:25:51 PM
BIOPHARMACEUTICS

Hae-Young Ahn
6/21/04 04:21:28 PM
BIOPHARMACEUTICS

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**21-687**	**Brand Name**	**Vytorin™**
OCPB Division (I, II, III)	**II**	**Generic Name**	**Ezetimibe/simvastatin combination**
Medical Division	**510**	**Drug Class**	**Lipid lowering**
OCPB Reviewer	**Wei Qiu, Ph.D.**	**Indication(s)**	**Primary hypercholesterolemia and homozygous familial hypercholesterolemia (HoFH)**
OCPB Team Leader	**Hae-Young Ahn**	**Dosage Form**	**Tablet**
		Dosing Regimen	**Ezetimibe 10 mg and simvastatin 10 mg, 20 mg, 40 mg or 80 mg**
Date of Submission	**24 Sept. 03**	**Route of Administration**	**Oral**
Estimated Due Date of OCPB Review	**June 16, 2004**	**Sponsor**	**MSP Singapore, LLC**
PDUFA Due Date	**July 24, 2004**	**Priority Classification**	**standard**
Division Due Date	**June 24, 2004**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				

alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	x	4		
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:	x			
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		4		

Filability and QBR comments

	"X" if yes	Comments
Application filable ?	x	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		The dissolution study was conducted in [redacted] phosphate buffer with [redacted] using USP apparatus II (paddle) [redacted] To optimize the dissolution method for quality control purpose as well as for granting biowaiver to strengths EZ10mg/Simva20 mg and EZ10 mg/Simva40 mg, the sponsor is recommended to investigate other two conditions such as at lower SLS level. The sponsor must submit dissolution profiles for all strength tablets from 3 batches under three different conditions
QBR questions (key issues to be considered)		Bioequivalence between EZ 10-mg/Simva 10-mg combination tablet and individual tablets of EZ 10-mg tablets and Simva 10-mg coadministered Bioequivalence between EZ 10-mg/Simva 80-mg combination tablet and individual tablets of EZ 10-mg tablet sand Simva 80-mg coadministered
Other comments or information not included above		Since the pivotal BE study is critical at bridging coadministration of individual tablets and combination tablet, it is desirable to conduct DSI inspection on pivotal study 039. **Clinical facilities:** **Site 001**: [redacted] **Site 003**. [redacted] 33142 **Analytical sites:** Merck Research Laboratories, West Point, PA 19486 (Plasma samples were analyzed for SV and SVA) [redacted] (Plasma samples were analyzed for unconjugated and total ezetimibe)
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

MSP Singapore Company, LLC (MSP), a joint venture between Merck & Co., Inc. and Schering Corporation submitted an NDA for VYTORINTM (ezetimibe/simvastatin combination tablets). The sponsor proposed four combination tablet strengths, with each strength containing ezetimibe 10 mg and simvastatin 10, 20, 40, and 80 mg, for the treatment of hypercholesterolemia and homozygous familial hypercholesterolemia (HoFH).

Clinical pharmacology section contains the following studies:

Pivotal study:
Protocol 039: Multicenter Study: An Open-Label, Randomized, 2-Part, 2-Period, Crossover Study to Evaluate the Definitive Bioequivalence After Concomitant Administration of Single Doses of Ezetimibe and Simvastatin as Individual

Tablets and as the Final Market Image of the Ezetimibe/Simvastatin 10/10 and 10/80 Fixed-Dose Combination Tablets in Healthy Adult Subjects

Pilot studies:

1. Protocol 020

[redacted] Clinical Study Report: An Open-Label, Randomized, 4-Period Crossover Study to Evaluate the Relative Oral Bioavailability of Simvastatin Plasma HMG-CoA Reductase Inhibitory Activity and Total Ezetimibe Following Single Oral Doses of Simvastatin and Ezetimibe Administered to Young Healthy Subjects as a Probe Fixed-Dose Combination Tablet Versus Concomitantly as Separate Entities

2. Protocol 024

[redacted], Clinical Study Report: An Open-Label, Randomized, 2-Period Crossover Study to Evaluate the Relative Oral Bioavailability of Simvastatin Based on Plasma HMG-CoA Reductase Inhibitory Activity and Ezetimibe Based on Total Ezetimibe Concentrations, Following Single Oral Doses of Simvastatin and Ezetimibe Administered to Young Healthy Subjects as a Probe Fixed-Dose Combination Tablet Versus Concomitantly as Separate Entities

3. Protocol 028

[redacted] Clinical Study Report: An Open-Label, Randomized, 2-Period Crossover Study to Evaluate the Relative Oral Bioavailability of Total Ezetimibe and Simvastatin and Simvastatin Acid Plasma Concentrations Following Single Oral Doses of Simvastatin and Ezetimibe Administered to Young Healthy Subjects as a Probe Fixed-Dose Combination Tablet Versus Concomitantly as Separate Entities

Study results of Protocol 039 showed that the EZ 10-mg/Simva 10-mg combination tablet was bioequivalent to individual tablets of EZ 10-mg tablet sand Simva 10-mg coadministered in terms of AUClast and Cmax of EZ and AUClast and Cmax of simvastatin acid.
EZ 10 mg/Simva 80-mg combination tablet was bioequivalent to individual tablets of EZ 10-mg tablet sand Simva 80-mg coadministered in terms of AUClast and Cmax of EZ and AUClast and Cmax of simvastatin acid.

Individual raw data and pharmacokinetic results are included.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Wei Qiu
10/28/03 02:49:11 PM
BIOPHARMACEUTICS

Hae-Young Ahn
10/31/03 10:17:23 AM
BIOPHARMACEUTICS